ORIGINAL ARTICLE

Regional Brain Metabolic Changes in Patients With Major Depression Treated With Either Paroxetine or Interpersonal Therapy

Preliminary Findings

Arthur L. Brody, MD; Sanjaya Saxena, MD; Paula Stoessel, PhD; Laurie A. Gillies, PhD; Lynn A. Fairbanks, PhD; Shervin Alborzian, BS; Michael E. Phelps, PhD; Sung-Cheng Huang, PhD; Hsiao-Ming Wu, PhD; Matthew L. Ho, BS; Mai K. Ho; Scott C. Au, BS; Karron Maidment, RN; Lewis R. Baxter, Jr, MD

Background: In functional brain imaging studies of major depressive disorder (MDD), regional abnormalities have been most commonly found in prefrontal cortex, anterior cingulate gyrus, and temporal lobe. We examined baseline regional metabolic abnormalities and metabolic changes from pretreatment to posttreatment in subjects with MDD. We also performed a preliminary comparison of regional changes with 2 distinct forms of treatment (paroxetine and interpersonal psychotherapy).

Methods: Twenty-four subjects with unipolar MDD and 16 normal control subjects underwent resting F 18 (^{18}F) fluorodeoxyglucose positron emission tomography scanning before and after 12 weeks. Between scans, subjects with MDD were treated with either paroxetine or interpersonal psychotherapy (based on patient preference), while controls underwent no treatment.

Results: At baseline, subjects with MDD had higher normalized metabolism than controls in the prefrontal cortex (and caudate and thalamus), and lower metabolism in the temporal lobe. With treatment, subjects with MDD had metabolic changes in the direction of normalization in these regions. After treatment, paroxetine-treated subjects had a greater mean decrease in Hamilton Depression Rating Scale score (61.4%) than did subjects treated with interpersonal psychotherapy (38.0%), but both subgroups showed decreases in normalized prefrontal cortex (paroxetine-treated bilaterally and interpersonal psychotherapy–treated on the right) and left anterior cingulate gyrus metabolism, and increases in normalized left temporal lobe metabolism.

Conclusions: Subjects with MDD had regional brain metabolic abnormalities at baseline that tended to normalize with treatment. Regional metabolic changes appeared similar with the 2 forms of treatment. These results should be interpreted with caution because of study limitations (small sample size, lack of random assignment to treatment groups, and differential treatment response between treatment subgroups).

Arch Gen Psychiatry. 2001;58:631-640

From the Departments of Psychiatry and Biobehavioral Sciences (Drs Brody, Saxena, Stoessel, Fairbanks, and Baxter; Messrs Alborzian, Ho, and Au; and Mss Ho and Maidment) and Medical and Molecular Pharmacology (Drs Phelps, Huang, Wu, and Baxter), University of California–Los Angeles, Los Angeles, Calif; Veterans Affairs Greater Los Angeles Health Care System (Dr Brody); Department of Psychiatry, University of Toronto, Toronto, Ontario (Dr Gillies); and Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham (Dr Baxter).

THE REGIONS most commonly found to be abnormal in functional brain imaging studies of major depressive disorder (MDD) are the prefrontal cortex (PFC), anterior cingulate gyrus (AC), and temporal lobe (TEMP).[1-4] Because there are reports of both increased and decreased activity in these structures in MDD, researchers have suspected that subregions of these structures have differentially altered function in MDD. Specifically, it has been hypothesized that dorsal brain structures (eg, dorsolateral prefrontal cortex [DLPFC]) have decreased activity,[1-3,5-7] while ventral structures (eg, ventrolateral prefrontal cortex [VLPFC] and ventral AC) have increased activity in the symptomatic depressed state.[3,5,6,8]

Studies examining activity change from before to after short-term medication treatment of MDD have generally found normalization of brain activity in the regions cited above.[3,9] The most commonly reported changes are in PFC. An increase in DLPFC metabolism has been reported with fluoxetine hydrochloride,[5]

See also pages 641, 649, and 651

sertraline hydrochloride,[10] and naturalistic treatment (with a variety of medications, including tricyclic antidepressants, lithium carbonate, benzodiazepines, and trazodone hydrochloride),[11,12] whereas a decrease in VLPFC (and anterior paralimbic) activity has been reported with paroxetine hydrochloride,[13] venlafaxine hydrochloride,[14] desipramine hydrochloride,[15] and electroconvulsive therapy.[16] Changes in the AC have been reported in a few studies, with

©2001 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 12/22/2014

SUBJECTS AND METHODS

SUBJECTS

Forty subjects (24 meeting *DSM-IV* criteria[19] for unipolar MDD and 16 normal controls) were recruited from a general psychiatry screening telephone service at the University of California–Los Angeles Neuropsychiatric Institute, Los Angeles, Calif, and from newspaper advertisements. An additional 3 subjects (1 in each MDD treatment subgroup and 1 normal control subject) underwent an initial scan, but dropped out before completion of other study parts needed for data analysis (eg, magnetic resonance [MR] imaging), so that their data were not used for the present study. The study was described to subjects, and written consent was obtained by means of a form approved by the University of California–Los Angeles Office for Protection of Research Subjects. Subjects were screened twice by a study physician (either A.L.B. or S.S.) before scanning. The Schedule for Affective Disorders and Schizophrenia–Lifetime version[20] was administered to confirm the diagnosis made via previous unstructured clinical interviews. Exclusion criteria were comorbid Axis I diagnoses (including substance abuse), concurrent medical conditions affecting brain function (such as neurologic conditions, eg, Parkinson disease), or medications with potential central nervous system side effects (eg, β-blockers). No subjects had taken psychotropic medications for at least 2 weeks (5 weeks for fluoxetine) before starting the study.

Symptom severity was measured at the time of both PET scans by a study investigator (A.L.B. or S.S., both psychiatrists trained in standardized assessment) using the 17-item Hamilton Depression Rating Scale (HAM-D),[21] Hamilton Anxiety Rating Scale,[22] Yale-Brown Obsessive-Compulsive Scale,[23] and Global Assessment of Functioning Scale.[24] In an attempt to minimize bias, subjects who underwent psychotherapy were not rated by their primary therapist. Percentage changes in rating scales were calculated by subtracting posttreatment scores from pretreatment scores, dividing by pretreatment scores, and multiplying by 100.

TREATMENT

Subjects with MDD were treated during the 12-week period between PET scans with either paroxetine (n=10) or IPT (n=14). Treatment type was determined by patient preference to enhance recruitment for this preliminary study, because many study recruits expressed a strong preference for either paroxetine or IPT. Normal control subjects underwent no treatment.

Paroxetine-treated patients initiated drug treatment on the day after the baseline PET scan, with dosage adjusted during 1 to 2 weeks to a target of 40 mg/d. No other psychotropic medications were allowed during the study period. Compliance was monitored by patient report during weekly 20-minute medication visits for the first 2 to 3 weeks and then monthly thereafter. Medication visits consisted of reviews of symptoms and side effects and titration of paroxetine dosage. Subjects received no formal psychotherapy during the medication trial.

Patients treated with IPT had 12 weekly psychotherapy sessions[17,25] with a trained IPT therapist (A.L.B. or P.S.), supervised by an experienced IPT supervisor (L.A.G.). Six subjects (3 for each therapist) had all psychotherapy sessions audiotaped and reviewed by the supervisor; these cases were then reviewed during weekly telephone sessions. The remaining cases were supervised as needed. The IPT was initiated during the week after baseline PET scanning. Subjects underwent 3 sessions during the first 2 weeks of treatment to have 12 psychotherapy sessions completed within the study time frame. Subjects treated with IPT who completed the trial were compliant with therapy (by patient report) and received no other psychotherapy and no psychoactive medication during the study. The foci of IPT were improvement of subjects' social networks and reduction of depressive symptoms. The primary problem foci of therapy (within the IPT model) were role transition (n=6), interpersonal dispute (n=3), social deficit (n=4), and grief (n=1).

MEASUREMENT OF REGIONAL GLUCOSE METABOLISM

Subjects underwent FDG-PET scanning at baseline and after 12 weeks. The FDG-PET method used in this study was similar to the method used in previous reports from our laboratory with separate groups of subjects,[13,18] except that all scans in the present study were obtained with a different tomograph (961 ECAT EXACT HR; Siemens-CTI, Knoxville, Tenn) in 2-dimensional mode and consisted of 47 transaxial slices. This technique yielded a resolution of 3.64 mm full-width at half-maximum at the center, with a 3.97-mm slice thickness.[26]

All subjects were scanned in the awake, resting state. Each subject's head was positioned with a standard head holder to minimize movement and ensure accuracy of placement in the tomograph. Scanning began with a 20-minute transmission scan with the use of 3 rotating germanium 68 rod sources for attenuation correction. Subjects then received an injection of 185 to 370 MBq of ^{18}F fluorodeoxyglucose. After a 40-minute uptake period, emission scanning was performed for 40 minutes. Scans were reconstructed from roughly 100 million counts.

PET DATA ANALYSIS

The PET data were analyzed with both statistical parametric mapping (SPM96)[27] and an MR imaging–based analysis of regions of interest (ROIs). Results from both methods were used and compared, given the limitations of each.[27-30]

For PET analysis with SPM96,[31-34] each subject's pair of images was realigned and coregistered, and all study images were reoriented within the program to the standardized coordinate system of Tailarach and Tournoux.[35] Global

dorsal increases and ventral decreases in activity being the most common findings.[5]

We obtained F 18 fluorodeoxyglucose (^{18}F) positron emission tomography (FDG-PET) scans in subjects with unipolar MDD both before and after treatment with either paroxetine or interpersonal psychotherapy (IPT).[17] (Normal control subjects were scanned in a similar time frame for comparison.) This data set was analyzed in 3 parts. First, we compared regional brain metabolism at baseline between the entire group of sub-

©2001 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 12/22/2014

normalization by proportional scaling was used. To adjust for differences in individual neuroanatomy and to improve the signal-to-noise ratio, a 10-mm full-width at half-maximum 3-dimensional gaussian smoothing filter was applied to all images.

To determine the location of SPM findings, PET scans and MR images of all study subjects were transformed into Tailarach space by means of the SPM program and significant regions were mapped onto group-averaged PET scans and MR images. Voxel coordinates were also located in the standard atlas.[35] No differences in anatomic assignment of region location were found between these methods.

For the MR imaging–based ROI analysis, each subject underwent MR imaging of the brain by means of a double-echo sequence (proton density and T2 images; repetition time, 2000-2500 milliseconds; echo time, 25-30 milliseconds and 90-110 milliseconds; 24-cm field of view; 3-mm slices with 0-mm separation). Coregistration of PET to MR images was performed with a 3-dimensional MR-PET image registration program.[36] The MR images were segmented into 4 different tissue types; image values were assigned with a relative proportion of 4:1:0:0.5 for gray matter, white matter, cerebrospinal fluid, and muscle, respectively. Segmented images were then smoothed 3-dimensionally to match the measured spatial resolution of PET data. The program then minimized the sum of squares of pixel value differences between PET and MR image sets to align measured FDG-PET images with the reconstructed MR image (the coregistration program used the Powell algorithm for minimization with 10 variable parameters).[37] The program then resliced the FDG-PET images to coregister within the 3-dimensional orientation of MR images.

The ROIs selected for analysis (**Figure 1**) on the basis of the literature cited above were DLPFC, VLPFC, and dorsal and ventral AC. Other ROIs chosen because of documented anatomic circuitry with the PFC and AC were the dorsal and ventral head of the caudate nucleus (Cd) and thalamus.[38-40] Both supratentorial whole hemispheres were also drawn to calculate ratios of ROI metabolism to overall metabolism in ipsilateral hemisphere. Normalized rather than absolute metabolic values were used for analysis, because absolute metabolic values (calculated from arterialized venous blood samples) were not thought to be adequately reliable. The ROIs were drawn on MR images by raters blind to subject identity (S.A., M.L.H., and M.K.H.) and reviewed at weekly meetings by 2 of us (A.L.B., S.S.) and the team of region drawers.

We elected not to delineate temporal lobe regions, because several different ones have been tentatively associated with MDD, and the boundaries of such structures are not reliably identifiable on transaxial MR images obtained.

Regions were drawn on each subject's MR image (Figure 1). The DLPFC and VLPFC were drawn in approximately 6 planes each and consisted of the dorsal and ventral halves of the middle frontal gyrus, respectively. The AC was divided into 6 dorsal and 6 ventral slices. The superior boundary of the AC was the base of the body of the cingulate gyrus, while the inferior boundary was gyrus rectus. The dorsal and ventral Cd regions (roughly 4 slices each) included the entire head of Cd and were drawn excluding the more posterior body of Cd. The entire thalamus was drawn in roughly 6 slices.

STATISTICAL ANALYSES

The data were screened for distributional properties, outliers, and missing values. No data were rejected by this process.

For both the SPM and MR imaging–based ROI analyses, 3 general steps were performed: (1) a comparison of baseline PET scans between the MDD and control groups, (2) a comparison of baseline to follow-up PET changes between the entire MDD and control groups, and (3) a preliminary analysis examining changes seen on PET from baseline to follow-up in the paroxetine-treated and IPT-treated subgroups.

In the SPM analyses, differences between baseline scans in the MDD and control groups were assessed with the Z statistic. Changes from baseline to follow-up were determined with Z values based on each subject's pair of scans within each group (normal control group, MDD group as a whole, paroxetine-treated subgroup, and IPT-treated subgroup). A threshold for significance of $P<.01$ was used for hypothesized regions. This threshold is similar or identical to that of other published studies using PET in MDD.[5,13,41-43] Results are presented by means of the voxel of peak significance.

For the MR imaging–based ROI analysis, baseline differences between the entire group of subjects with MDD and normal controls were determined with an overall multivariate analysis of variance with the use of hypothesized ROI (DLPFC, VLPFC, dorsal and ventral AC and Cd, and thalamus) and laterality (left and right) as within-group factors and group (MDD vs normal control) as a between-subject factor (SPSS version 8.0; SPSS Inc, Chicago, Ill). Based on a significant result indicating regional differences between subjects with MDD and control subjects, t tests (2-tailed, uncorrected) were performed to determine which regions accounted for the overall difference between subjects with MDD and normal control subjects. Changes from baseline to follow-up in normalized ROI values were compared between subjects with MDD and normal control subjects by means of change in ROI scores in only regions found to be abnormal at baseline and a t test for independent means (2-tailed). To examine the relationship between symptomatic change and ROI change, Kendall τ correlations (2-tailed) were performed between 17-item HAM-D change and regional metabolic change for the MDD group. Finally, in an exploratory analysis, normalized regional brain metabolic changes for hypothesized ROIs in both subgroups of subjects with MDD (paroxetine-treated and IPT-treated) were compared with brain metabolic change values for normal control subjects by means of a t test for independent means. The α levels were set at $P=.05$.

jects with MDD and the normal control group, hypothesizing that DLPFC metabolism would be decreased and ventral prefrontal and paralimbic metabolism increased in subjects with MDD compared with normal control subjects, as has been reported previously.[1-6,8] Second, brain metabolic changes from baseline to follow-up in the whole group of subjects with MDD were compared with changes seen in normal control subjects. We hypothesized that, in subjects with MDD, DLPFC metabolism would increase significantly,

©2001 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 12/22/2014

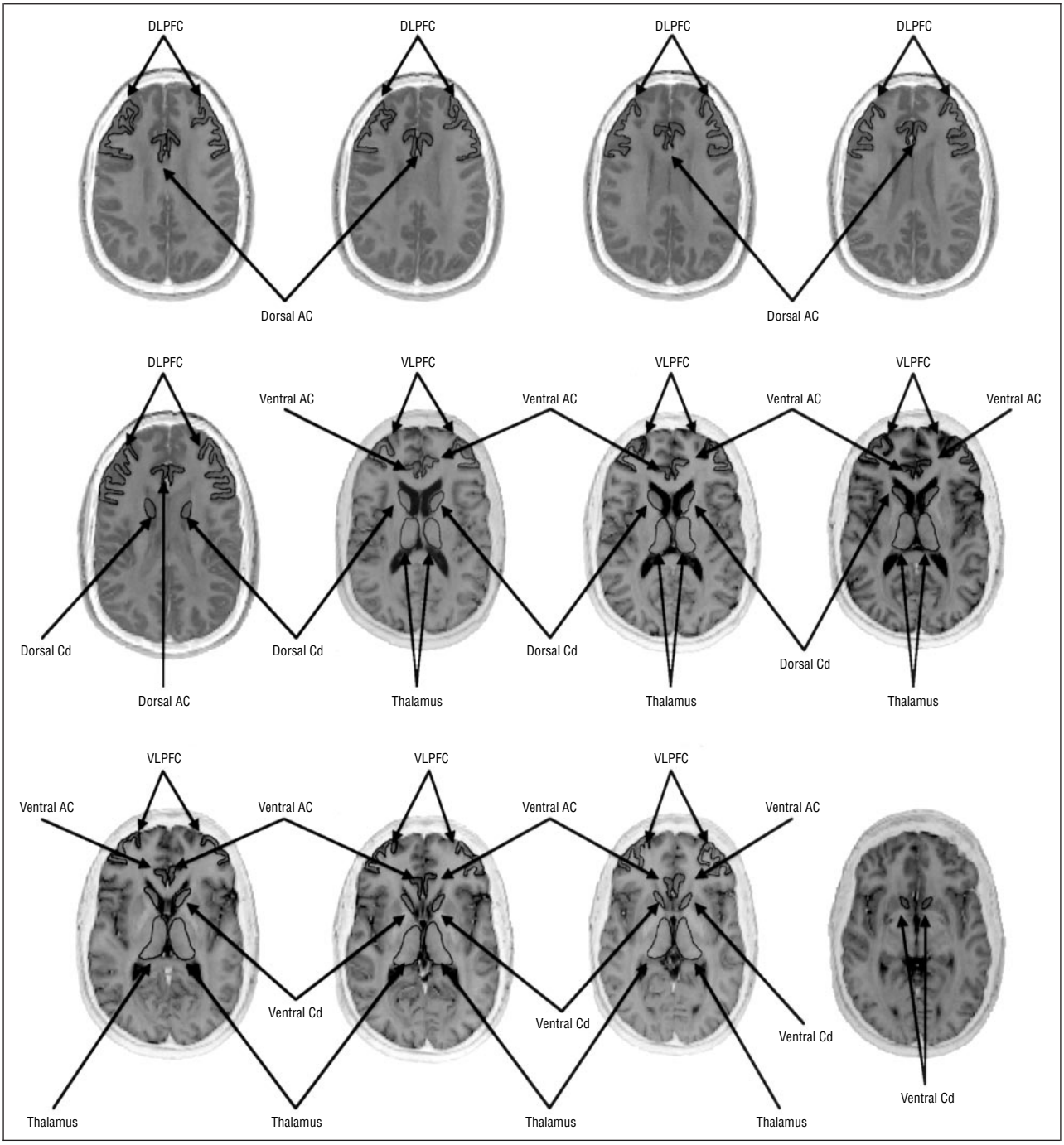

Figure 1. Regions of interest drawn on a magnetic resonance image of a study subject for transfer onto coregistered positron emission tomography scans. DLPFC indicates dorsolateral prefrontal cortex; AC, anterior cingulate gyrus; VLPFC, ventrolateral prefrontal cortex; and Cd, head of the caudate nucleus.

whereas VLPFC (and other ventral prefrontal and limbic) metabolism would decrease significantly with treatment compared with changes in normal control subjects. Third, we performed a preliminary comparison of brain metabolic changes between the 2 subgroups of subjects with MDD (paroxetine-treated and IPT-treated), hypothesizing that brain metabolic changes found with the 2 forms of treatment would be similar, as has been reported with medication (fluoxetine) and psychotherapy (cognitive behavioral therapy) for obsessive-compulsive disorder.[18]

RESULTS

CLINICAL FINDINGS

The normal control and MDD groups were similar in age, sex distribution, and time frame between PET scans (**Table 1**). From before to after treatment, the total MDD group and both MDD subgroups (paroxetine-treated and IPT-treated) had significant mean decreases in the 17-item HAM-D (paired *t* test, 2-tailed, all $P<.001$), while control subjects did not

©2001 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 12/22/2014

Table 1. Clinical Variables of Study Population*

Clinical Variable	Normal Control Subjects (n = 16)	MDD Group: Total (N = 24)	MDD Group: Paroxetine-Treated (n = 10)	MDD Group: IPT-Treated (n = 14)
Sex, % F	50	54	50	57
Age, y	35.6 ± 18.3	38.9 ± 11.4	36.4 ± 12.2	40.7 ± 11.0
Time between scans, wk	12.7 ± 3.0	12.5 ± 3.3	11.6 ± 2.3	13.1 ± 3.9
No. of previous treatment trials	NA	2.9 ± 1.9	2.3 ± 1.6	3.3 ± 2.1
FH of MDD, %	0	54.2	40.0	64.3
Age at onset of MDD, y	NA	20.3 ± 9.6	21.5 ± 11.0	19.4 ± 8.8
HAM-D				
Pretreatment	0.8 ± 1.3	19.4 ± 5.4	17.8 ± 5.5	20.5 ± 5.3
Posttreatment	1.3 ± 1.6	9.8 ± 5.1	5.8 ± 2.1	12.6 ± 4.7
% Change	NA	–47.8 ± 26.0	–61.4 ± 28.3	–38.0 ± 19.9
HAM-A				
Pretreatment	1.4 ± 1.5	17.3 ± 6.2	16.0 ± 7.7	18.1 ± 5.1
Posttreatment	1.9 ± 1.6	10.7 ± 6.3	6.4 ± 4.3	13.8 ± 5.8
% Change	NA	–35.2 ± 37.3	–55.5 ± 36.3	–20.8 ± 31.7
Y-BOCS				
Pretreatment	0	1.8 ± 5.0	3.1 ± 6.9	0.8 ± 2.9
Posttreament	0	1.4 ± 3.5	1.4 ± 3.8	1.4 ± 3.5
% Change	NA	NA	NA	NA
GAF				
Pretreament	90.9 ± 3.2	48.7 ± 5.5	49.0 ± 5.7	48.4 ± 5.6
Postreatment	89.0 ± 4.9	66.5 ± 11.6	74.4 ± 9.5	60.9 ± 9.8
% Change	NA	38.0 ± 26.3	53.6 ± 24.8	26.8 ± 22.0

*MDD indicates major depressive disorder; IPT, interpersonal psychotherapy; NA, not applicable; FH, family history of MDD in first-degree relative; HAM-D,17-item Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; and GAF, Global Assessment of Functioning Scale. Values are mean ± SD unless otherwise specified.

have a significant mean change in 17-item HAM-D. Within the MDD group, the paroxetine-treated subgroup was less ill at baseline (lower HAM-D score, fewer previous treatments for depression, less family history, later mean age at onset) and had greater improvement on all symptom rating scales than the IPT-treated subgroup (Table 1).

COMPARISONS OF BASELINE METABOLISM BETWEEN SUBJECTS WITH MDD AND CONTROL SUBJECTS

At baseline, SPM demonstrated that subjects with MDD had higher relative metabolism than control subjects in left (Z=3.72; x, y, z coordinates: x=–44, y=24, z=30) and right (Z=3.44; x=40, y=38, z=18) PFC (at the border of DLPFC and VLPFC, roughly corresponding to Brodmann areas 9 and 46), left (Z=3.04; x=–16, y=4, z=16) and right (Z=2.66; x=14, y=–4, z=14) dorsal Cd, and left (Z=3.35; x=–14, y=–24, z=8) and right (Z=3.47; x=14, y=–24, z=4) thalamus (**Figure 2**). This analysis also showed lower relative pretreatment activity in left (Z=3.21; x=–42, y=8, z=–16) and right (Z=3.25; x=28, y=18, z=–32) anterior inferior TEMP for subjects with MDD.

In the ROI-based analysis, the overall multivariate analysis of variance disclosed a significant ROI × laterality × group interaction ($F_{6,33}$=2.46; P<.05), indicating that individual regions differed between the MDD and control groups. In examining individual ROIs at baseline, the group of subjects with MDD had significantly higher normalized metabolism in right DLPFC, left VLPFC, right dorsal Cd, and bilateral thalamus than normal control subjects (**Table 2**). Baseline differences for other regions did not reach significance.

METABOLIC CHANGES FROM BASELINE TO FOLLOW-UP

From pretreatment to posttreatment, SPM showed decreases in normalized left PFC metabolism in separate regions slightly anterior and posterior to the region found to be elevated at baseline (**Table 3** and **Figure 3**). Statistical parametric mapping also showed decreases in right PFC metabolism, including regions that overlapped with those found elevated at baseline (Table 3). In addition, increases in left insula and bilateral inferior TEMP were found in the total MDD group (Table 3). Normal control subjects did not have these changes other than an increase in normalized right inferior TEMP metabolism.

Of the regions found abnormal at baseline in the ROI analysis, only the right dorsal Cd decreased significantly in the MDD group compared with normal control subjects from baseline to follow-up (Table 2). Change in normalized left thalamic metabolism was significantly correlated with change in HAM-D (τ=0.30; P=.04).

PRELIMINARY COMPARISON OF METABOLIC CHANGES WITH PAROXETINE AND IPT

The SPM analysis of changes from baseline to follow-up in MDD subgroups treated with either paroxetine or IPT showed several similarities (Table 3 and **Figure 4**). In the paroxetine-treated subgroup, normalized metabo-

©2001 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 12/22/2014

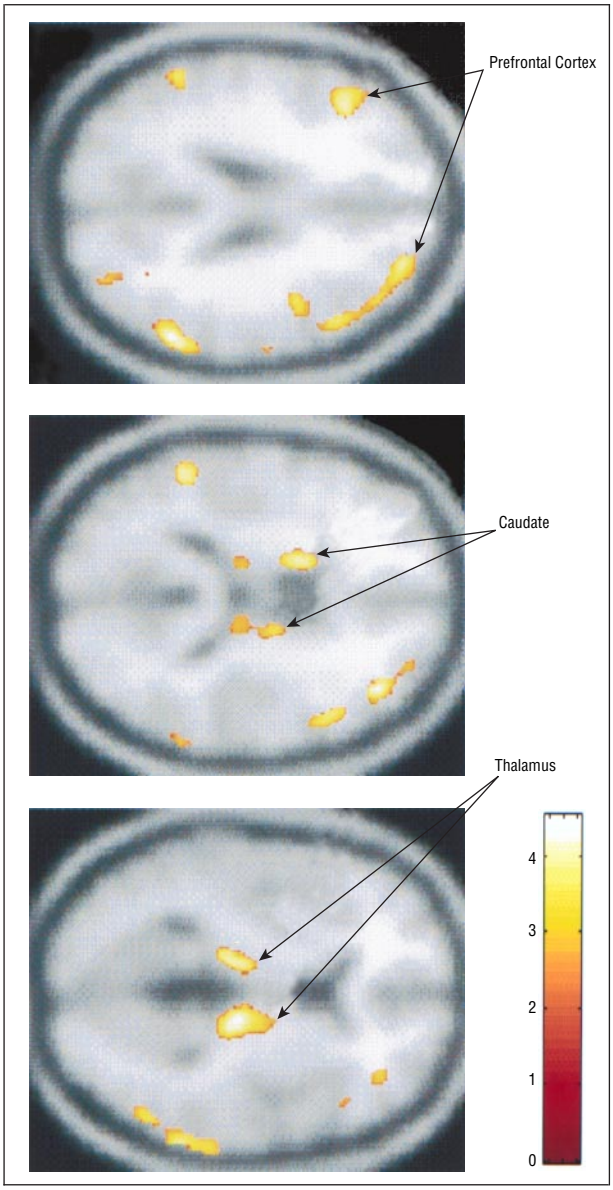

Figure 2. Baseline comparison of the major depressive disorder (MDD) (N=24) and normal control (n=16) groups, showing regions of elevated normalized metabolism (*Z* statistic, *P*<.01) in the MDD group mapped onto a template magnetic resonance image.

lism decreased in the middle frontal gyrus (including the VLPFC and DLPFC) and left ventral AC, and increased in left TEMP and right insula. In the IPT-treated subgroup, normalized metabolism significantly decreased in right middle frontal gyrus (including both VLPFC and DLPFC) and left middle AC, and increased in left TEMP and anterior insula. Although the insula was not a hypothesized ROI, results are included because they were the most statistically significant result in both subgroups. Normal control subjects had no significant changes in these regions (Table 3).

In the ROI-based comparison of metabolic changes between subjects with MDD in the 2 treated subgroups and normal control subjects, each treated subgroup showed a significant decrease in right dorsal Cd metabolism compared with control subjects (change in ROI value: paroxetine-treated, –0.03±0.06; IPT-treated, –0.04±0.08; normal control, 0.02±0.05) (2-tailed *t* test, paroxetine-treated vs normal control, $df=24$, $P=.03$; IPT-treated vs control, $df=28$, $P=.008$). Normalized left VLPFC metabolism also decreased significantly in paroxetine-treated patients compared with control subjects (change in ROI value: paroxetine-treated, –0.04±0.03; normal control, 0.00±0.06) (*t* test, $df=24$, $P=.05$).

COMMENT

Subjects with MDD had regional brain metabolic abnormalities at baseline that appeared to change in the direction of normalization with treatment. The central findings here of increased relative PFC, Cd, and thalamic metabolism in subjects with MDD at baseline that decreased from pretreatment to posttreatment is consistent with earlier studies having similar findings.[3,5,8,13] The portions of VLPFC found to be abnormal here and to decrease with treatment are similar to those found to be abnormal in earlier work (see Drevets,[3] Table 1) and to change with selective serotonin reuptake inhibitors.[13,14] The finding in the present study of increased normalized DLPFC metabolism that decreases with treatment (as opposed to the converse of these findings reported by others)[5,10-12] may be due to the fact that this study examined ambulatory outpatients with MDD, whereas inpatients with MDD were examined in the majority of previous studies.[5,11,12] Such subjects may have had profound differences in symptoms from outpatients studied here (eg, greater suicidality, less mood reactivity, and more psychomotor retardation). A link between decreased DLPFC activity and psychomotor retardation has been reported previously.[44]

In the preliminary comparison of brain metabolic changes with either paroxetine or IPT, similar regional brain metabolic changes were found in treated patients with MDD that were different from those seen in normal control subjects scanned and rescanned during the same time frame. On SPM, relative PFC and left AC metabolism decreased and relative left TEMP metabolism increased in both treated MDD subgroups. The decrease in middle (IPT-treated subgroup) and ventral (paroxetine-treated subgroup) AC activity (roughly corresponding to slightly different parts of Brodmann area 32 for the 2 subgroups) was similar, but more dorsal, to the subgenual AC decrease (Brodmann area 25) previously found to change from pretreatment to posttreatment with fluoxetine.[5] In addition, both subgroups had a regional increase in insular metabolism (right-sided for the paroxetine subgroup and left-sided for the IPT subgroup) as the most statistically significant finding. In contrast, the normal control group did not have these changes. Relative stability of frontal-subcortical brain circuitry from test to retest in normal control subjects undergoing 2 FDG-PET scans has also been demonstrated by others.[45,46]

In the ROI analysis, normalized right dorsal Cd metabolic rates decreased in both treated subgroups compared with control subjects. These similarities occurred despite there being a difference in HAM-D improvement with the 2 forms of treatment, perhaps indicating that both subgroups had similar changes in symptoms

©2001 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 12/22/2014

Table 2. Normalized ROI Values for the Control and MDD Groups*

ROI	Control Group (n = 16)		MDD Group (N = 24)		Baseline Comparison (*df* = 38)		Baseline to Follow-up (*df* = 38)	
	Baseline	Follow-up	Baseline	Follow-up	*t*	*P*	*t*	*P*
Dorsal Cd								
Right	1.16 ± 0.07	1.18 ± 0.09	1.23 ± 0.08	1.20 ± 0.09	**–2.9**	**.007**	**3.0**	**.005**
Left	1.17 ± 0.07	1.16 ± 0.07	1.21 ± 0.08	1.19 ± 0.08	–1.3	.20	0.3	.78
Ventral Cd								
Right	1.17 ± 0.07	1.17 ± 0.07	1.20 ± 0.07	1.18 ± 0.09	–1.1	.27	0.7	.49
Left	1.21 ± 0.07	1.20 ± 0.09	1.23 ± 0.07	1.20 ± 0.08	–1.0	.33	0.7	.47
Dorsal AC								
Right	1.11 ± 0.06	1.11 ± 0.05	1.14 ± 0.08	1.12 ± 0.07	–1.3	.19	1.4	.17
Left	1.11 ± 0.07	1.10 ± 0.06	1.11 ± 0.07	1.10 ± 0.05	0.2	.86	–0.4	.70
Ventral AC								
Right	1.09 ± 0.08	1.07 ± 0.09	1.10 ± 0.08	1.07 ± 0.10	–0.2	.82	0.3	.75
Left	1.05 ± 0.10	1.08 ± 0.11	1.10 ± 0.08	1.10 ± 0.08	–1.4	.17	1.0	.32
DLPFC								
Right	1.21 ± 0.06	1.21 ± 0.05	1.25 ± 0.05	1.23 ± 0.06	**–2.0**	**.05**	1.4	.16
Left	1.22 ± 0.07	1.21 ± 0.06	1.25 ± 0.06	1.23 ± 0.05	–1.8	.08	0.9	.36
VLPFC								
Right	1.15 ± 0.08	1.16 ± 0.07	1.17 ± 0.08	1.16 ± 0.08	–0.8	.43	1.3	.21
Left	1.14 ± 0.07	1.14 ± 0.06	1.18 ± 0.06	1.16 ± 0.06	**–2.4**	**.02**	1.6	.12
Thalamus								
Right	1.05 ± 0.05	1.02 ± 0.08	1.08 ± 0.05	1.07 ± 0.07	**–2.0**	**.05**	–0.6	.53
Left	1.03 ± 0.07	1.02 ± 0.06	1.09 ± 0.07	1.06 ± 0.07	**–2.7**	**.01**	0.9	.40

*ROI indicates region of interest; MDD, major depressive disorder; Cd, head of the caudate nucleus; AC, anterior cingulate gyrus; DLPFC, dorsolateral prefrontal cortex; and VLPFC, ventrolateral prefrontal cortex. Boldface type indicates statistically significant values.

Table 3. Statistical Parametic Mapping Analysis Showing Regional Changes (*P*<.01, Uncorrected) in the MDD and Normal Control Groups*

ROI	MDD Group: Total (N = 24)				MDD Group: Paroxetine-Treated (n = 10)				MDD Group: IPT-Treated (n = 14)				Normal Control Subjects (n = 16)			
		Coordinates				Coordinates				Coordinates				Coordinates		
	Z	x	y	z	*Z*	x	y	z	*Z*	x	y	z	*Z*	x	y	z
Decreases																
PFC																
Left	3.66	–20	62	4	3.83	–50	28	24	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
	3.30	–62	16	10	3.61	–62	14	8								
Right	3.35	32	54	–4	3.74	36	50	20	3.53	40	2	58	. . .	. . .	. . .	. . .
	3.25	22	40	40	3.34	8	54	38	2.79	38	10	30				
	2.75	42	8	30	3.25	8	60	–10	4.29	30	50	–14				
AC, left	. . .	. . .	. . .	. . .	3.40	–10	52	2	3.13	–2	22	34	. . .	. . .	. . .	. . .
TEMP, left	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	2.92	–30	–4	–44
Increases																
Insula																
Left	3.36	–28	26	12	. . .	. . .	. . .	. . .	4.90	–46	20	8	. . .	. . .	. . .	. . .
	3.28	–36	6	18												
Right	. . .	. . .	. . .	. . .	4.29	38	–18	8	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
TEMP																
Left	4.06	–36	–34	–2	3.39	–36	–32	–6	3.63	–34	4	–18	. . .	. . .	. . .	. . .
									3.06	–38	–60	–18				
Right	3.40	36	–42	2	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	3.19	54	–24	8

*MDD indicates major depressive disorder; IPT, interpersonal psychotherapy; ROI, region of interest; PFC, prefrontal cortex; AC, anterior cingulate gyrus; TEMP, temporal lobe; and ellipses, insignificant findings.

not well measured with the HAM-D (such as improved social functioning). However, only the paroxetine-treated group showed a significant decrease in right VLPFC, which has been found previously to correlate with improvement in HAM-D scores in paroxetine-treated subjects.[13] This difference might reflect the more robust improvement in the paroxetine-treated subgroup.

The most important limitation of this study was sample size. A larger, more diverse sample may have improved detection of changes not reaching significance and

©2001 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 12/22/2014

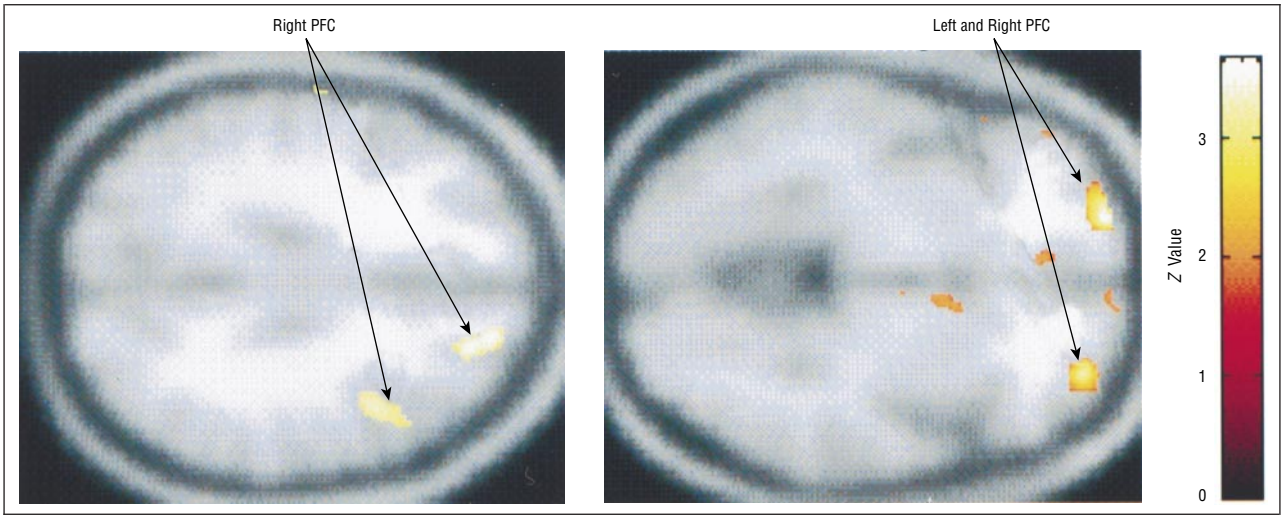

Figure 3. Decreases in relative prefrontal cortical (PFC) metabolism from baseline to follow-up in the total major depressive disorder (MDD) treated group (N=24) (*Z* statistic, *P*<.01). Decreases in activity are transposed onto a template magnetic resonance image and are shown in 2 separate planes.

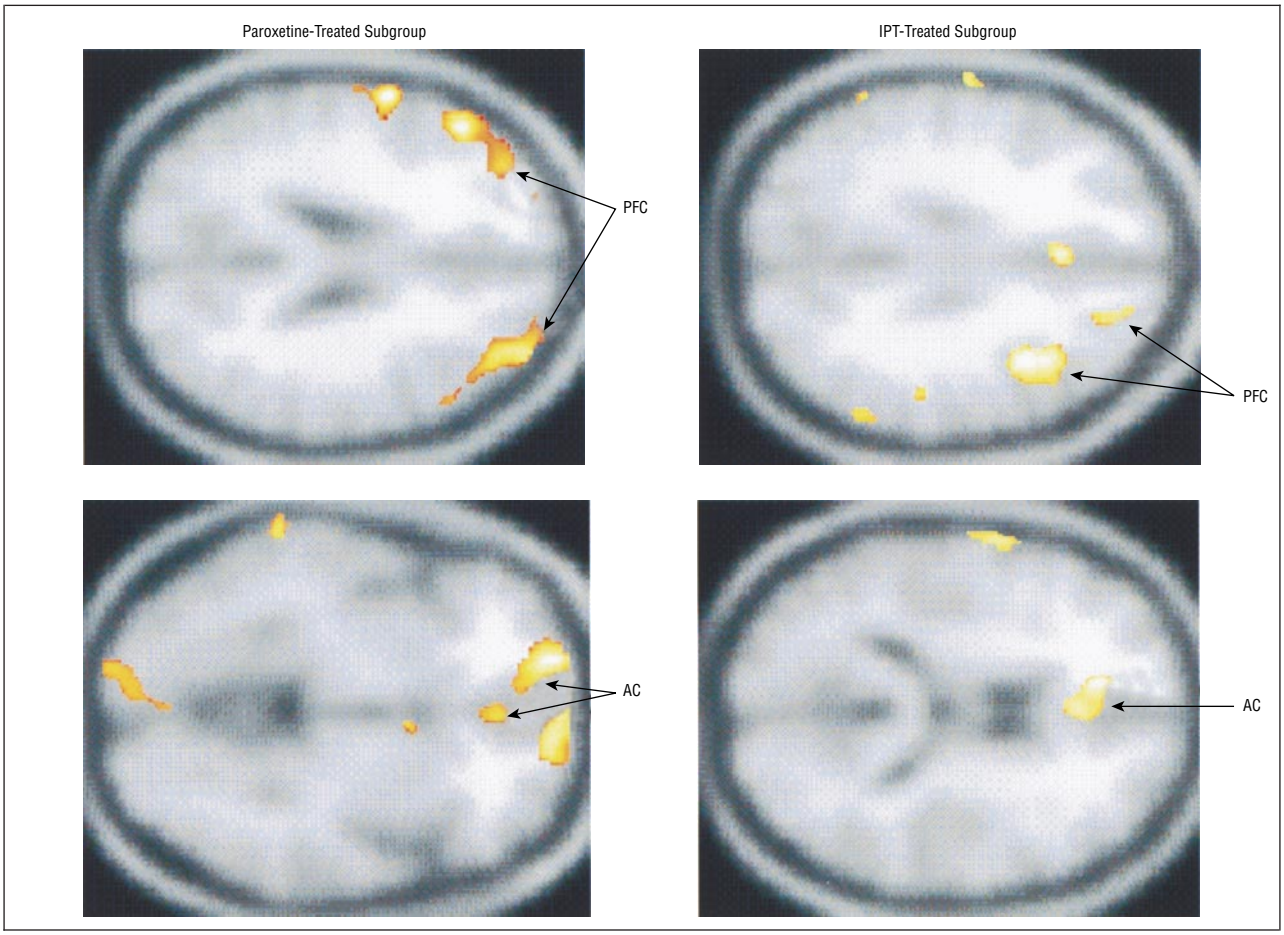

Figure 4. Comparison of relative brain metabolic decreases (*Z* statistic, *P*<.01) from baseline to follow-up in major depressive disorder subgroups treated with either paroxetine (n=10) or interpersonal psychotherapy (IPT) (n=14). The paroxetine-treated subgroup showed bilateral prefrontal cortical (PFC) decreases, while the IPT-treated subgroup had changes in right PFC only. Both groups had decreases in left anterior cingulate gyrus (AC).

enhanced power to detect responder-nonresponder differences (the paroxetine-treated subgroup having an unusually high response rate here and the IPT-treated subgroup having an unusually low response rate [likely because of a greater severity of illness][47]). A second limitation was the lack of random assignment to treatment subgroups. Because of this limitation, there may have been fundamental differences between subjects who chose one form of therapy vs the other that may have accounted for both clinical (Table 1) and brain metabolic differ-

©2001 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 12/22/2014

ences. A third limitation was the use of subjects without comorbid Axis I illnesses. While the study population examined herein has the advantage of making the data more clearly interpretable (without confounding illnesses affecting regional glucose metabolism), it limits the degree to which study results are generalizable (given that MDD is a highly comorbid illness).[48] Finally, the lack of reliable blood curve data (as might have been obtained from arterial blood samples) meant that absolute glucose metabolic rates could not be determined; global metabolic activity may have an important role in MDD. These limitations require that study results (especially for the comparison of paroxetine vs IPT) be regarded as suggestive and need confirmation in a randomized study with a greater sample size.

Our results are consistent with the putative mechanism of action of selective serotonin reuptake inhibitors. Short-term treatment with selective serotonin reuptake inhibitors has been found to desensitize serotonin autoreceptors (somatodentritic serotonin$_{1a}$ and terminal serotonin$_{1b/d}$).[49,50] This desensitization leads to enhanced serotonin release in the PFC.[51,52] Serotonin agonism in the PFC has been linked to increased extracellular γ-aminobutyric acid levels from γ-aminobutyric acid–containing interneurons,[53] which may explain the changes seen in this study with short-term paroxetine treatment, as specific γ-aminobutyric acid interneurons exert powerful inhibitory control over excitatory neurons in the PFC.[54] Serotonin also has been shown to directly reduce glutamatergic responses in cortex.[55] The AC has similarly strong serotonergic innervation.[56] Modulation of frontal-subcortical brain circuits could also explain changes seen in Cd (presumably receiving lower levels of excitatory glutamatergic input from PFC and AC[38,39,51]). Thus, this study supports the hypothesis that selective serotonin reuptake inhibitors lead to an attenuation of PFC (and AC)–basal ganglia–thalamic brain circuit activity that mediates MDD symptomatology.[57,58]

While less is known about the mechanism of action of IPT, it has been hypothesized that psychotherapy in general (as a learning experience) leads to changes in synaptic plasticity,[59,60] through a retraining of implicit memory systems.[59,61] Because a focus of IPT is improved socialization, areas of the brain associated with socialization may undergo an attenuation of neuronal connectivity during IPT. For example, increased activity in the cingulate cortex (and related structures) has been associated with distress when an animal is socially isolated.[62,63] This model may be analogous to the socially isolated subject with MDD who has a decrease in AC activity as socialization improves with IPT. This change could be the result of enhancement of the serotonergic system, as has been hypothesized for behavioral therapy for obsessive-compulsive disorder.[64]

Other significant changes seen in subjects with MDD (increases in relative activity in TEMP and insula) may represent either normalization of depression-related baseline dysfunction or compensatory changes related to brain regions found to decrease in activity, given that both TEMP and insula have strong reciprocal connections with PFC and AC regions that decreased in activity with treatment.[8,40,65]

Accepted for publication July 28, 2000.

This study was supported by the National Alliance for Research in Schizophrenia and Depression, Great Neck, NY (Dr Brody); a Veterans Affairs Advanced Research Career Development Award, Washington, DC (Dr Brody); the Charles A. Dana Foundation Consortium on Neuroimaging Leadership, New York, NY (Dr Saxena); grant R01 MH-53565 from the National Institute of Mental Health, Bethesda, Md (Dr Baxter); and US Department of Energy (Washington) grants AM03-76-SF00012 and DE-FCO3-87-ER 60615 (Drs Phelps, Huang, and Baxter).

Presented in part at the American College of Neuropsychopharmacology Annual Meeting, Acapulco, Mexico, December 14, 1999.

We thank Lori L. Altshuler, MD, Magnus Dahlbom, PhD, and Mark A. Mandelkern, MD, PhD, for their suggestions on the manuscript.

Corresponding author and reprints: Arthur L. Brody, MD, 300 UCLA Medical Plaza, Suite 2340, Los Angeles, CA 90095 (e-mail: abrody@ucla.edu).

REFERENCES

1. Ketter TA, George MS, Kimbrell TA, Benson BE, Post RM. Functional brain imaging, limbic function and affective disorders. *Neuroscientist*. 1996;2:55-65.
2. Kennedy SH, Javanmard M, Vaccarino FJ. A review of functional neuroimaging in mood disorders: positron emission tomography and depression. *Can J Psychiatry*. 1997;42:467-475.
3. Drevets WC. Functional neuroimaging studies of depression: the anatomy of melancholia. *Annu Rev Med*. 1998;49:341-361.
4. Byrum CE, Ahearn EP, Krishan K. A neuroanatomic model for depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 1999;23:175-193.
5. Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, Silva JA, Tekell JL, Martin CC, Lancaster JL, Fox PT. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am J Psychiatry*. 1999;156:675-682.
6. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. *J Neuropsychiatry*. 1997;9:471-481.
7. Baxter LR, Saxena S, Brody AL, Ackermann RF, Colgan M, Schwartz JM, Allen-Martinez Z, Fuster JM, Phelps ME. Brain mediation of obsessive-compulsive disorder symptoms: evidence from functional brain imaging studies in the human and non-human primate. *Semin Clin Neuropsychiatry*. 1996;1:32-47.
8. Drevets WC. Prefrontal cortical-amygdalar metabolism in major depression. In: McGinty JF, ed. *Advancing from the Ventral Striatum to the Extended Amygdala: Implications for Neuropsychiatry and Drug Use: In Honor of Lennart Heimer*. New York: New York Academy of Sciences; 1999:614-637.
9. Rubin E, Sackeim HA, Nobler MS, Moeller JR. Brain imaging studies of antidepressant treatment. *Psychiatr Ann*. 1994;24:653-658.
10. Buchsbaum MS, Wu J, Siegel BV, Hackett E, Trenary M, Abel L, Reynolds C. Effect of sertraline on regional metabolic rate in patients with affective disorder. *Biol Psychiatry*. 1997;41:15-22.
11. Baxter LR, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, Gerner RH, Sumida RM. Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Arch Gen Psychiatry*. 1989;46:243-250.
12. Martinot J-L, Hardy P, Feline A, Huret J-D, Mazoyer B, Attar-Levy D, Pappata S, Syrota A. Left prefrontal glucose hypometabolism in the depressed state: a confirmation. *Am J Psychiatry*. 1990;147:1313-1317.
13. Brody AL, Saxena S, Silverman DHS, Alborzian S, Fairbanks LA, Phelps ME, Huang S-C, Wu H-M, Maidment K, Baxter LR. Brain metabolic changes in major depressive disorder from pre- to post-treatment with paroxetine. *Psychiatry Res Neuroimaging*. 1999;91:127-139.
14. Little JT, Ketter TA, Kimbrell TA, Danielson A, Benson BE, Willis MW, Dunn RT, Frye MA, Post RM. Anterior paralimbic blood flow decreased after venlafaxine response. *Biol Psychiatry*. 1997;41(suppl 7):79S-80S.
15. Drevets WC, Raichle ME. Neuroanatomical circuits in depression: implications for treatment mechanisms. *Psychopharmacol Bull*. 1992;28:261-274.
16. Nobler MS, Sackheim HA, Prohovnik I, Moeller JR, Mukherjee S, Schnur DB, Prudic J, Devanand DP. Regional cerebral blood flow in mood disorders, III: treatment and clinical response. *Arch Gen Psychiatry*. 1994;51:884-897.

©2001 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 12/22/2014

17. Klerman GL, Weissman MM, Rounsaville BJ, Chevron ES. *Interpersonal Psychotherapy of Depression*. New York, NY: Basic Books; 1984.
18. Baxter LR, Schwartz JM, Bergman KS, Szuba MP, Guze BH, Mazziotta JC, Alazraki A, Selin CE, Ferng HK, Munford P, Phelps ME. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1992;49:681-689.
19. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.
20. Spitzer RL, Endicott J. *Schedule for Affective Disorders and Schizophrenia*. New York: New York State Psychiatric Institute; 1978.
21. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Psychol*. 1967;6:278-296.
22. Hamilton M. Diagnosis and rating of anxiety. *Br J Psychiatry*. 1969;3:76-79.
23. Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Heninger GR, Charney DS. The Yale-Brown Obsessive-Compulsive Scale, I: development, use, and reliability. *Arch Gen Psychiatry*. 1989;46:1006-1011.
24. Endicott J, Spitzer RL, Fleiss JL, Cohen J. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry*. 1976;33:766-771.
25. Weissman MM, Markowitz JC. Interpersonal psychotherapy: current status. *Arch Gen Psychiatry*. 1994;51:599-606.
26. Wienhard K, Dahlbom M, Eriksson L, Michel C, Bruckbauer T, Pietrzyk U, Heiss WD. The ECAT EXACT HR: performance of a new high-resolution positron scanner. *J Comput Assist Tomogr*. 1994;18:110-118.
27. Friston KJ, Worsley KJ, Frackowiak RSJ, Mazziotta JC, Evans AC. Assessing the significance of focal activations using their spatial extent. *Hum Brain Mapp*. 1994; 1:214-220.
28. Nadeau SE, Crosson B. A guide to functional imaging of cognitive processes. *Neuropsychiatry Neuropsychol Behav Neurol*. 1995;8:143-162.
29. Rajkowska G, Goldman-Rakic PS. Cytoarchitectonic definition of prefrontal areas in the normal human cortex, II: variability in locations of areas 9 and 46 and relationship to the Tailarach coordinate system. *Cereb Cortex*. 1995;5: 323-337.
30. Steinmetz H, Seitz RJ. Functional anatomy of language processing: neuroimaging and the problem of individual variability. *Neuropsychologia*. 1991;29:1149-1161.
31. Friston K, Frith C, Liddle P, Frackowiak R. Comparing functional (PET) images: the assessment of significant change. *J Cereb Blood Flow Metab*. 1991;11:690-699.
32. Friston KJ. Statistical parametric mapping: ontology and current issues. *J Cereb Blood Flow Metab*. 1995;15:361-370.
33. Friston KJ, Ashburner J, Frith CD, Poline J, Heather JD, Frackowiak RSJ. Spatial registration and normalisation of images. *Hum Brain Mapp*. 1995;2:165-189.
34. Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp*. 1995;2:189-210.
35. Tailarach J, Tournoux P. *Co-planar Stereotaxic Atlas of the Human Brain*. New York, NY: Thieme Medical Publishers Inc; 1988.
36. Lin KP, Huang S-C, Baxter LR, Phelps ME. A general technique for inter-study registration of multi-function and multimodality images. *IEEE Trans Nucl Sci*. 1994; 41:2850-2855.
37. Press WH, Flannery BP, Teukolsky SA, Vetterling WT. *Numerical Recipes*. New York, NY: Cambridge University Press; 1986.
38. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci*. 1986;9: 357-381.
39. Parent A, Hazrati L-N. Functional anatomy of the basal ganglia, I: the cortico-basal ganglia-thalamo-cortical loop. *Brain Res Rev*. 1995;20:91-127.
40. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. *Brain*. 1995;118:279-306.
41. Marangell LB, Ketter TA, George MS, Pazzaglia PJ, Callahan AM, Parekh P, Andreason PJ, Horwitz B, Herscovitch P, Post RM. Inverse relationship of peripheral thyrotropin-stimulating hormone levels to brain activity in mood disorders. *Am J Psychiatry*. 1997;154:224-230.
42. Ketter TA, Andreason PJ, George MS, Lee C, Gill DS, Parekh PI, Willis MW, Herscovitch P, Post RM. Anterior paralimbic mediation of procaine-induced emotional and psychosensory experiences. *Arch Gen Psychiatry*. 1996;53:59-69.
43. Sargent PA, Kjaer KH, Bench CJ, Rabiner EA, Messa C, Meyer J, Gunn RN, Grasby PM, Cowen PJ. Brain serotonin$_{1A}$ receptor binding measured by positron emission tomography with [^{11}C]WAY-100635: effects of depression and antidepressant treatment. *Arch Gen Psychiatry*. 2000;57:174-180.
44. Dolan RJ, Bench CJ, Liddle PF, Friston KJ, Frith CD, Grasby PM, Frackowiak RS. Dorsolateral prefrontal cortex dysfunction in the major psychoses: symptom or disease specificity? *J Neurol Neurosurg Psychiatry*. 1993;56:1290-1294.
45. Goldman S, Dethy S, Lotstra F, Biver F, Stanus E, Wikler D, Hildebrand J, Mendlewicz J, Luxen A. Basal ganglia and frontal lobe glucose metabolism: a reproducibility positron emission tomography study. *J Neuroimaging*. 1995;5:219-226.
46. Stapleton JM, Morgan MJ, Liu X, Yung BC, Phillips RL, Wong DF, Shaya EK, Dannals RF, London ED. Cerebral glucose utilization is reduced in second test session. *J Cereb Blood Flow Metab*. 1997;17:704-712.
47. Elkin I, Gibbons RD, Shea MT, Sotsky SM, Watkins JT, Pilkonis PA, Hedeker D. Initial severity and differential treatment outcome in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *J Consult Clin Psychol*. 1995;63:841-847.
48. Blazer DG, Kessler RC, McGonagle KA, Swartz MS. The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. *Am J Psychiatry*. 1994;151:979-986.
49. Blier P, Pineyro G, El Mansari M, Bergeron R, De Montigny D. Role of somatodendritic 5-HT autoreceptors in modulating 5-HT neurotransmission. In: Martin GR, Eglen RM, Hoyer D, Hamblin MW, Yocca F, eds. *Advances in Serotonin Receptor Research: Molecular Biology, Signal Transduction, and Therapeutics*. New York: New York Academy of Sciences; 1998:204-216.
50. Bergqvist PBF, Bouchard C, Blier P. Effect of long-term administration of antidepressant treatments on serotonin release in brain regions involved in obsessive-compulsive disorder. *Biol Psychiatry*. 1999;45:164-174.
51. el Mansari M, Bouchard C, Blier P. Alteration of serotonin release in the guinea pig orbito-frontal cortex by selective serotonin reuptake inhibitors: relevance to treatment of obsessive-compulsive disorder. *Neuropsychopharmacology*. 1995; 13:117-127.
52. Blier P, de Montigny C. Serotonin and drug-induced therapeutic responses in major depression, obsessive-compulsive and panic disorders. *Neuropsychopharmacology*. 1999;21(suppl 2):91S-98S.
53. Abi-Saab WM, Bubser M, Roth RH, Deutch AY. 5-HT$_2$ receptor regulation of extracellular GABA levels in the prefrontal cortex. *Neuropsychopharmacology*. 1999; 20:92-96.
54. Lewis DA, Pierri JN, Volk DW, Melchitzky DS, Woo TW. Altered GABA neurotransmission and prefrontal cortical dysfunction in schizophrenia. *Biol Psychiatry*. 1999;46:616-626.
55. Sizer AR, Kilpatrick GJ, Roberts MH. A post-synaptic depressant modulatory action of 5-hydroxytryptamine on excitatory amino acid responses in rat entorhinal cortex in vitro. *Neuropharmacology*. 1992;31:531-539.
56. Crino PB, Morrison JH, Hof PR. Monoaminergic innervation of cingulate cortex. In: Vogt BA, Gabriel M, eds. *Neurobiology of Cingulate Cortex and Limbic Thalamus: A Comprehensive Handbook*. Boston, Mass: Birkhaeuser; 1993:285-310.
57. Swerdlow NR. Serotonin, obsessive-compulsive disorder and the basal ganglia. *Int Rev Psychiatry*. 1995;7:115-129.
58. Feifel D. Neurotransmitters and neuromodulators in frontal-subcortical circuits. In: Miller BL, Cummings JL, eds. *The Human Frontal Lobes: Functions and Disorders*. New York, NY: Guilford Press; 1999:174-186.
59. Liggan DY, Kay J. Some neurobiological aspects of psychotherapy: a review. *J Psychother Pract Res*. 1999;8:103-114.
60. Post RM, Weiss SR. Emergent properties of neural systems: how focal molecular neurobiological alterations can affect behavior. *Dev Psychopathol*. 1997;9: 907-929.
61. Amini F, Lewis T, Lannon R, Louie A, Baumbacher G, McGuinness T, Schiff EZ. Affect, attachment, memory: contributions toward psychobiologic integration. *Psychiatry*. 1996;59:213-239.
62. Panksepp J, Nelson E, Bekkedal M. Brain systems for the mediation of social separation-distress and social-reward: evolutionary antecedents and neuropeptide intermediaries. In: Carter CS, Lederhendler II, Kirkpatrick B, eds. *The Integrative Neurobiology of Affiliation*. New York: New York Academy of Sciences; 1997:78-100.
63. Kyuhou S, Gemba H. Two vocalization-related subregions in the midbrain periaqueductal gray of the guinea pig. *Neuroreport*. 1998;9:1607-1610.
64. Baer L. Behavior therapy: endogenous serotonin therapy? *J Clin Psychiatry*. 1996; 57(suppl 6):33-35.
65. Augustine JR. Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Res Rev*. 1996;22:229-244.

©2001 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 12/22/2014